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(54) **STABLE OIL-IN-WATER EMULSIONS INCORPORATING A TAXINE (TAXOL) AND METHOD OF MAKING SAME**

ÖL-IM-WASSER-EMULSIONEN ENTHALTEND TAXIN (TAXOL) UND VERFAHREN

EMULSIONS STABLES HUILE-DANS-EAU INCORPORANT UNE TAXINE (TAXOL) ET PROCEDE DE PREPARATION

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- **DATABASE WPI Week 9339, Derwent Publications Ltd., London, GB; AN 93-309115 (39) & JP,A,05 221 852 (LTT KENKYUSHO KK) 31 August 1993**

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Description

Field of the Invention

[0001] This invention relates to the class of compounds known as taxines and, more particularly, to formulations of taxines (taxol) for intravenous infusion.

Background of the Invention

[0002] Taxol, a member of the class of compounds known as taxines, comes from the bark of the Pacific yew tree, *Taxus brevifolia*, and has been found useful in the treatment of various cancers. For example, taxol has been used in treating ovarian, breast, non-small cell lung, and head and neck carcinomas. David M. Peereboom et al., "Successful Re-Treatment with Taxol After Major Hypersensitivity Reactions", Journal of Clinical Oncology, 11 (5), pp. 885-890 (1993). One of the difficulties in administering taxol is that the drug is insoluble in water. The present state of the art in taxol formulation requires a 50:50 mixture of Cremophor-EL surfactant (polyoxyethylated castor oil) and ethanol in order to solubilize the drug. Unfortunately, this taxol formulation leads to a relatively high incidence of major hypersensitivity reactions (HSRs) upon intravenous administration. These HSRs have been attributed to the unusually high concentration of Cremophor-EL required to solubilize the taxol. Id.

[0003] There have been other attempts to provide a taxol formulation, the most successful of which has been incorporation of the drug into a liposomal formulation. However, this preparation suffers from the fact that it is difficult to achieve a quantitative incorporation of the drug into the liposomal compartment. Furthermore, the product must be lyophilized and stored as a powder because taxol precipitates from aqueous liposomal formulations within a week of storage. For this reason, the liposomal formulation must be freeze dried and reconstituted prior to use.

[0004] Attempts to formulate taxol in a stable lipid emulsion have been unsuccessful. Taxol is reported to be insoluble in lipid emulsions such as Intralipid®, which contains soybean oil, or Liposyn®, which contains a mixture of soybean and safflower oils. L.C. Collins-Gold et al., "Parenteral Emulsions for Drug Delivery", Advanced Drug Delivery Reviews, 5, pp. 189-208 (1990). Heating taxol in either soybean oil or safflower oil, even upon sonication, does not result in the dissolution of appreciable amounts of taxol, and addition of taxol to a lipid emulsion during the homogenization step meets with equally disappointing results. Emulsions incorporating up to 15 mg/ml of taxol have been formulated with triacetin, L-α-lecithin, Polysorbate 80, Pluronic F-68, ethyloleate and glycerol. However, these emulsions are highly toxic and unstable. B. Tarr et al., "A New Parenteral Emulsion for the Administration of Taxol", Pharmaceutical Research, 4, pp. 162-165 (1987).

[0005] Therefore, there is a clear need for a stable, easily prepared, biocompatible, efficacious formulation of a taxine such as taxol exhibiting minimal side effects.

Summary of the Invention

[0006] The present invention provides a composition for intravenous administration of taxine in a stable oil-in-water emulsion comprising a taxine; a triglyceride; water; and a surfactant, wherein said taxine is solubilized in said triglyceride in an effective pharmaceutical amount for intravenous administration, said taxine and triglyceride forming a stable dispersed phase in the water.

[0007] The invention also provides a method of incorporating a taxine into a triglyceride comprising the steps of dissolving a taxine in a solution of said triglyceride and a co-solvent for said taxine; and removing said co-solvent to form a solution of said taxine in said triglyceride.

[0008] The composition includes a taxine, a triglyceride, water and a surfactant. More particularly, a taxine such as taxol is solubilized in an oil which is a triglyceride or rich in triglycerides in an effective pharmaceutical amount for intravenous administration. The taxine and oil mixture forms a dispersed phase in the water. Other taxines include taxotere, spicatin and others as hereinafter disclosed.

[0009] Preferably, the oil is an oil rich in triglycerides, such as safflower oil, soybean oil or mixtures thereof. Because taxol is more soluble in safflower oil than soybean oil, safflower oil is most preferred. The surfactant used may be any of a number of surfactants, and usually is a phospholipid such as lecithin.

[0010] Typically, the taxine is present in an amount of about 0.1% to about 1% by weight of the emulsion, while the oil is present in an amount of from about 1% to about 40% and the surfactant is present in an amount of about 0.5% to about 5% by weight of the emulsion.

[0011] If desired, the composition may further include various additives. For example, glycerin may be added to adjust the osmolarity of the composition. Most commonly, sufficient glycerin (typically 0.5-5% by weight) is added to attain an osmolarity of between 280 and 320 milliosomoles per liter, but more or less may be added to achieve a hyperosmolar or hypoosmolar solution, depending on the desired end use.

[0012] Other common additives such as xylitol, mannitol, dextrose or lactated Ringer's solution may be added to the formulation, again depending on the desired end use.

[0013] Sterols such as cholesterol, or long chain (C_{14} - C_{22}) alcohols may be optionally added as co-solubilization agents. If used, such agents typically represent about 1% or less by weight of the emulsion.

[0014] The taxine may be incorporated at various concentrations, with 5 mg taxine/ml of emulsion being a typical concentration.

[0015] The invention also is directed to a method of incorporating a taxine into a triglyceride. The method includes dissolving a taxine in a solution of the triglyceride and a co-solvent for the taxine, and removing the taxine co-solvent to form a solution of the taxine in triglyceride. The taxine co-solvent enables the taxine to be solubilized in the triglyceride and preferably is a short chain alcohol, such as methanol, ethanol or isopropanol. The alcohol may be removed by a number of different methods such as evaporation and the like. The triglyceride is provided by an oil which is a triglyceride or is rich in triglycerides.

[0016] A preferred embodiment involves a method for formulating a taxine in a stable oil-in-water emulsion. After forming a taxine and oil solution, the solution is dispersed in water with a surfactant to form a stable oil-in-water emulsion.

[0017] An advantage of the inventive composition and methods is the formation of a stable taxine-in-oil emulsion. Another advantage is that the taxine formulation is efficacious yet exhibits minimal side effects. Furthermore, the inventive formulation may be easily prepared and is biocompatible with several common additives.

Detailed Description of the Invention

A. Taxine

[0018] Taxine formulations of the invention include a taxine, an oil, water and a surfactant. The term "taxine" as used in the literature and herein is meant to include the alternative forms of nomenclature such as "taxane". Examples of taxines which may be used include taxol (paclitaxel); taxotere; spicatin; taxane-2, 13-dione, 5.beta., 9.beta., 10.beta.-trihydroxy-, cyclic 9, 10-acetal with acetone, acetate; taxane-2, 13-dione, 5.beta., 9.beta., 10.beta.-trihydroxy-,cyclic 9, 10-acetal with acetone; taxane-2.beta., 5.beta., 9.beta., 10.beta.-tetrol, cyclic 9, 10-acetal with acetone; taxane; cephalomannine-7-xyloside; 7-epi-10-deacetylcephalomannine; 10-deacetylcephalomannine; cephalomannine; taxol B; 13-(2', 3'-dihydroxy-3'-phenylpropionyl)baccatin III; yunnanxol; 7-(4-Azidobenzoyl)baccatin III; N-debenzoyltaxol A; O-acetylbaccatin IV; 7-(triethylsilyl)baccatin III; 7,10-Di-O-[(2,2,2-trichloroethoxy)carbonyl]baccatin III; baccatin III 13-O-acetate; baccatin diacetate; baccatin; baccatin VII; baccatin VI; baccatin IV; 7-epi-baccatin III; baccatin V; baccatin I; baccatin III; baccatin A; 10-deacetyl-7-epitaxol; epitaxol; 10-deacetyltaxol C; 7-xylosyl-10-deacetyltaxol; 10-deacetyltaxol-7-xyloside; 7-epi-10-deacetyltaxol; 10-deacetyltaxol; and 10-deacetyltaxol B.

B. Oil

[0019] The term "oil" is used herein in a general sense to identify a large class of physiologically acceptable substances each of which is a triglyceride or is rich in triglycerides whether of mineral, vegetable, animal, essential or synthetic origin. In the classification of oils by type or function, for example, vegetable oils are chiefly derived from seeds or nuts and include semidrying oils such as safflower and soy bean oils. A liquid fatty oil which is a triglyceride is the preferred oil. Medium chain triglycerides also serve as useful oils according to this invention.

C. Surfactant

[0020] A surfactant is needed to form stable emulsions. Any suitable surfactant may be employed alone or in combination with other surfactants. For example, egg yolk phospholipids such as lecithin or Pluronics emulsifying agents may be used. Pluronics agents are block polymer polyols sold by Wyandotte, e.g., Pluronics F68, having a molecular weight of about 8,000, may be employed. Ethoxylates of cholesterol, diacyl glycerol and dialkyl ether glycerol are useful surfactants. Also, using backbones of cholesterol, diacyl glycerol or dialkyl ether glycerol, block copolymers are made by adding ethylene oxide, propylene oxide and ethylene oxide, in that order, in varying amounts to produce surfactants. The emulsions of this invention may contain alkylphosphoryl choline or alkylglycerophosphoryl choline surfactants described in Kaufman and Richard, U.S. Ser. No. 791,420, filed November 13, 1991. Specific examples of these surfactants are 1,2-dioctylglycero-3-phosphoryl choline, 1,2-ditetradecylglycero-3-phosphoryl choline, 1,2-dihexadecylglycero-3-phosphoryl choline, 1,2-dioctadecylglycero-3-phosphoryl choline, 1-hexadecyl-2tetradecylglycero-3-phosphoryl choline, 1-octadecyl-2-tetradecylglycero-3-phosphoryl choline, 1-tetradecyl-2-octadecylglycero-3-phosphoryl choline, 1-hexadecyl-2-octadecylglycero-3-phosphoryl choline, 1-2-dioctadecylglycero-3-phosphoryl choline, 1-octadecyl-2-hexadecylglycero-3-phosphoryl choline, 1-tetradecyl-2-hexadecylglycero-3-phosphoryl choline, 2,2-ditetradecyl-1-phosphoryl choline ethane and 1-hexadecyl-tetradecylglycero-3-phosphoryl choline. The 1,3-dialkyl glycerophos-

phoryl choline surfactants as described in Kaufman and Richard, U.S. Serial No. 08/228,224, filed April 15, 1994, may also be used. Mixtures of these novel surfactants with other known surfactants may also be employed. Anionic surfactants include alkyl or aryl sulfates, sulfonates, carboxylates or phosphates. Cationic surfactants include such as mono-, di-, tri- and tetraalkyl or aryl ammonium salts. Non-ionic surfactants include alkyl or aryl compounds, whose hydrophilic part consists of polyoxyethylene chains, sugar molecules, polyalcohol derivatives or other hydrophilic groups. Zwitter-ionic surfactants may have a combination of the above anionic or cationic groups, and whose hydrophobic part consists of any other polymer, such as polyisobutylene or polypropylene oxides.

D. Preferred Taxine Formulation and Method

[0021] A preferred taxine formulation according to the principles of the invention is prepared by dissolving taxol (paclitaxel) in an alcohol solution. If desired, the optional sterol co-additive, such as cholesterol, may be added to this same alcohol solution. This solution is then added to an equivalent volume of oil and mixed until clear. The alcohol is then removed by rotary evaporation or evaporation under a stream of nitrogen.

[0022] A phospholipid, such as egg yoke lecithin, is dispersed into water, which may optionally contain glycerin for the purpose of achieving the desired osmolarity. In fact, glycerin may be added to the aqueous phase at any point during processing. While continuing to stir the dispersion at high speed, the oil solution containing taxol (and cholesterol or glycerin if desired) is added to the dispersion, forming a crude emulsion. The resulting crude emulsion is refined by cycling through a homogenizer, resulting in a shelf stable, small particle size, non-toxic emulsion suitable for intravenous administration. These and other objectives of this invention will be further understood with reference to the following nonlimiting examples.

Example 1

Preparation of Lipid Emulsions of Taxol

[0023] A solution of 15 mg taxol/ml and 20 mg cholesterol/ml in isopropanol was prepared. This solution was added to an equal volume of safflower oil, and the alcohol was removed, either by rotary evaporation or by evaporation under a stream of nitrogen. This resulted in a safflower oil solution containing 15 mg taxol/ml and 20 mg cholesterol/ml.

[0024] 1.9 g egg yolk lecithin was dispersed in 61 ml water using an Ultraturrax high speed mixer. Stirring continued at high speed while 32 ml of the safflower oil solution containing taxol (15 mg/ml) and cholesterol (20 mg/ml) were slowly added to the dispersion. The resulting crude emulsion was refined by cycling through a homogenizer for 20 minutes at a pressure of 8000 pounds per square inch. A Microfluidizer homogenizer was used to allow for work at small volumes. However, standard homogenization equipment, such as Gaulin homogenizers are expected to work equally well since they are commonly used in the large scale preparation of fat emulsions used in parenteral nutrition.

[0025] The resulting aqueous emulsion had the composition shown in Table 1, column 1. In order to compare stabilities, four additional formulations were prepared by the same method, and the compositions of these emulsions also are shown in Table. 1.

TABLE 1

EMULSION	1	2	3	4	5
Lecithin	2.0%	2.0%	2.0%	2.0%	2.0%
Safflower Oil	33.3%	33.4%	33.3%	33.5%	33.6%
Glycerin	0.0%	0.0%	2.0%	0.0%	1.9%
Cholesterol	0.67%	0.67%	0.67%	0.0%	0.0%
Taxol	0.51%	0.00%	0.51%	0.51%	0.5%

Example 2

Stability of Lipid Emulsions of Taxol

[0026] The five different taxol formulations presented in Table 1 above were subjected to an accelerated aging study of six weeks duration at 40°C. Stability measurements included taxol concentration, pH, viscosity and mean particle size. The results of the study are presented in Tables 2A-E.

TABLE 2A

EMULSION 1	0 WEEKS	2 WEEKS	4 WEEKS*	6 WEEKS
Taxol %	0.46	0.45	0.47	0.44
pH	7.38	6.80	5.13	6.88
Osmolarity (mOsm/L)				
Viscosity (cP)	3.21	2.91	10.0	3.59
Mean Particle Size (μm)	0.367	0.317	0.740	0.360

* This particular 4 week sample is an outlier sample, as is confirmed by the values at 6 weeks.

TABLE 2B

EMULSION 2	0 WEEKS	2 WEEKS	4 WEEKS	6 WEEKS
Taxol %	0.00	0.00	0.00	0.00
pH	8.01	6.98	7.06	6.36
Osmolarity (mOsm/L)				
Viscosity (cP)	3.62	3.42	3.54	3.59
Mean Particle Size (μm)	0.268	0.237	0.326	0.317

TABLE 2C

EMULSION 3	0 WEEKS	2 WEEKS	4 WEEKS	6 WEEKS
Taxol %	0.45	0.44	0.45	0.45
pH	6.65	7.07	7.02	6.56
Osmolarity (mOsm/L)	357	360	358	362
Viscosity (cP)	3.61	2.91	3.34	4.14
Mean Particle Size (μm)	0.308	0.368	0.348	0.322

TABLE 2D

EMULSION 4	0 WEEKS	2 WEEKS	4 WEEKS	6 WEEKS
Taxol %	0.47	0.45	0.46	0.46
pH	7.83	7.22	6.84	6.51
Osmolarity (mOsm/L)				
Viscosity (cP)	3.12	3.11	3.02	3.34
Mean Particle Size (μm)	0.322	0.295	0.315	0.315

TABLE 2E

EMULSION 5	0 WEEKS	2 WEEKS	4 WEEKS	6 WEEKS
Taxol %	0.39	0.41	0.44	0.42
pH	8.06	7.29	6.73	6.88
Osmolarity (mOsm/L)	344	332	342	343
Viscosity (cP)	2.92	2.62	2.82	3.07

TABLE 2E (continued)

EMULSION 5	0 WEEKS	2 WEEKS	4 WEEKS	6 WEEKS
Mean Particle Size (μm)	0.291	0.278	0.299	0.308

[0027] The taxol concentration remained relatively constant throughout the course of the study. The differences between the charged amount of taxol (0.51%) and the amount listed in the stability studies is due to the difficulty in maintaining accurate water balance during the preparation of such small scale emulsions (the homogenizer tubing contains significant dead volume). In support of this contention, the high performance liquid chromatographic analysis of taxol, from which the stability values are derived, showed no evidence of significant taxol degradation over the entire course of the study. In addition, microscopic examination (1200x magnification) demonstrated that taxol had not precipitated or crystallized from the sample.

[0028] As is the case with all triglyceride emulsions used clinically, there was a mild, biologically insignificant reduction in pH as the samples aged. Viscosity showed no statistically significant variation and was well below the range of human blood (9-12 cP). In addition, particle size was relatively constant over time, further demonstrating the stability of the lipid emulsions of taxol.

Example 3

Admixture With Common Clinical Fluids

[0029] For clinic utility of products intended for intravenous use, it is important to determine whether or not common additives such as 5% dextrose or lactated Ringer's solution can be co-administered or mixed with the products. To this end, separate samples of emulsions 4 and 5 of Table 1 were diluted with dextrose or lactated Ringer's solution at two different concentrations (1:1 and 1:4 dilutions), and the samples were held at 25°C for 24 hours and subsequently analyzed for mean particle size by laser light scattering using a Brookhaven Model BI-90. Mean particle size values before and after add mixture are shown in Table 3. These results indicate that the liquid emulsions of taxol are very stable to admixture with fluids commonly used in the clinical environment.

TABLE 3

	Before Mixin g	1:1 Dextros e	1:4 Dextrose	1:1 Lactated Ringer's	1:4 Lactated Ringer's
Emulsion 4	0.295	0.313	0.322	0.329	0.309
Emulsion 5	0.278	0.293	0.267	0.301	0.294

Example 4

Toxicity of the Lipid Emulsion of Taxol Relative to the Traditional Taxol-Cremophor Formulation

[0030] 15 white Sprague-Dawley rats were divided into three groups with five animals in each group. One group served as a control and received no treatment. The second and third groups were infused with the inventive lipid emulsion and the commercially available taxol-Cremophor formulation, respectively. Prior to administration, the emulsion and Cremophor formulation were diluted to a final concentration of 1 mg taxol/ml according to the package insert for "Taxol® (paclitaxel) for Injection Concentrate", using 0.9% saline. Then the treatment group animals were infused with a dose of 42 mg/kg (42 cc/kg of diluted material) over the space of 1/2 hour. The animals were monitored for survival, organ weights, hematology and clinical chemistry at 14 days post infusion. Survival and normalized organ weight (grams per 100 grams body weight) data are displayed in Table 4.

TABLE 4

	Survival	Liver	Lung	Spleen	Testes	Thymus
Control	5/5	4.45	0.49	0.32	1.09	0.29
Emulsion	4/5	4.78	0.52	0.52	0.72	0.15
taxol-Cremophor Formulation	0/5					

[0031] All animals in the taxol-Cremophor formulation treatment group were ataxic and unresponsive to stimuli im-

mediately upon infusion, and all were dead within 24 hours. In sharp contrast, all animals from the emulsion group exhibited normal behavior from the point of infusion onward. However, the animals in this group did exhibit weight loss during the first few days, and one of them died approximately four days after infusion. In comparing the weights of the emulsion treatment group with those of the control, the liver and lung weights all are within experimental error for different lots of animals. However, it appears that the spleens are slightly enlarged in the treatment group, while the testes and thymus are slightly smaller.

[0032] Blood samples were withdrawn by heart stick from the animals treated with the lipid emulsion, and the samples were analyzed for hematological and clinical chemistry parameters, with the results shown in Tables 5 and 6 respectively. The hematological and clinical chemistry results were within normal limits for a random rodent population. Surprisingly, the expected taxol-induced thrombocytopenia was not observed. It may be that the platelet population was restored over the extended 14 day time of the study.

TABLE 5

HEMATOLOGY							
WBC (th/mm^3)	RBC (mil/mm^3)	HGB (g/dl)	HCT (vol%)	MCV μm^3	MCH (pg)	MCHC (%)	Neut. (#/mm^3)
7325	5.43	12.0	36.1	66.5	22.2	33.5	1558
Bands (#/mm^3)	Lymphs (#/mm^3)	Monos (#/mm^3)	Eos (#/mm^3)	Basos (#/mm^3)	nRBC (#/mm^3)	Platelets (#/mm^3)	Retics (#/mm^3)
78	5522	74	0	0	0	1427000	290460

TABLE 6

CLINICAL CHEMISTRY							
Glucose (mg/dl)	Nitrogen (mg/dl)	Creat (mg/dl)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Ca (mg/dl)	P (mg/dl)
232	21	0.5	144	6.8	102	10.9	11.9
UA (mg/dl)	Chol (mg/dl)	TG (mg/dl)	Bili (mEq/L)	BiliD (mEq/L)	Bilil (mEq/L)	AP (U/L)	SGOT (U/L)
1.5	69	63	0.2	0.0	0.2	450	100
SGPT (U/L)	GGTP (U/L)	LDH (U/L)	Protein (g/dl)	Albumin (g/dl)	Glob (g/dl)	A/G (ratio)	Fe (µg/dl)
59	<1	578	5.6	3.4	2.1	1.6	229

Example 5

Efficacy

[0033] In order to test the efficacy of the lipid emulsion of taxol, the emulsion was screened against both the Cremophor excipient containing no taxol and the commercial taxol-Cremophor formulation. The three samples were tested in two different cell lines. The cell lines employed were mouse lymphocytic leukemia (L1210) in Fisher's medium containing 10% horse serum, and rat mammary adenocarcinoma (NMU) in MEM medium containing 10% fetal bovine serum. For each cell line, 10 ml of medium was inoculated with 10^6 cells. The lymphocytic leukemia line was incubated for 16 hours, and the mammary adenocarcinoma line was incubated for 24 hours. After incubation, the cells were stained with Trypan blue, and the viable cells were counted with a hemacytometer. It is important to note that absorption techniques could not be employed because of the turbidity of the emulsion. In addition, agar diffusion was not applicable since emulsion particles diffuse at a different rate than the commercially formulated solution. The results for each line are presented in Tables 7A and 7B.

[0034] The data show that the Cremophor excipient containing no taxol is itself somewhat toxic to the cell lines employed. Otherwise, there appear to be no significant differences between the commercial taxol formulation and the inventive lipid emulsion of taxol.

TABLE 7A

MOUSE LYMPHOCYTIC LEUKEMIA			
	Cremophor Excipient	Emulsion	taxol-Cremophor
0.01 µg/ml	121	45.1	52.8
0.1 µg/ml	126	39.1	37.0
1.0 µg/ml	147	33.1	36.2
10 µg/ml	3.2	35.2	2.8

TABLE 7B

RAT MAMMARY ADENOCARCINOMA			
	Cremophor Excipient	Emulsion	taxol-Cremophor
0.01 µg/ml	95.21	81.4	89.9
0.1 µg/ml	91.7	36.8	40.8
1.0 µg/ml	108	28.7	35.1
10 µg/ml	48.0	20.8	24.8

[0035] Other modifications of this invention may be made without departing from its scope as will be understood to a person of ordinary skill in this art.

Claims

1. A composition for intravenous administration of taxine in a stable oil-in-water emulsion comprising:

   a taxine;
   a triglyceride;
   water; and
   a surfactant, wherein said taxine is solubilized in said triglyceride in an effective pharmaceutical amount for intravenous administration, said taxine and triglyceride forming a stable dispersed phase in the water.

2. A composition according to claim 1 wherein said taxine is selected from the group consisting of taxol; taxotere; spicatin; taxane-2, 13-dione, 5.beta., 9.beta., 10.beta.-trihydroxy-,cyclic 9, 10-acetal with acetone, acetate; taxane-2, 13-dione, 5.beta., 9.beta., 10.beta.-trihydroxy-, cyclic 9, 10-acetal with acetone; taxane-2.beta., 5.beta., 9.beta., 10.beta.-tetrol, cyclic 9, 10-acetal with acetone; taxane; cephalomannine-7-xyloside; 7-epi-10-deacetylcephalomannine; 10-deacetylcephalomannine; cephalomannine; taxol B; 13-(2', 3'-dihydroxy-3'-phenylpropionyl)baccatin III; yunnanxol; 7-(4-Azidobenzoyl)baccatin III; N-debenzoyltaxol A; O-acetylbaccatin IV; 7-(triethylsilyl)baccatin III; 7,10-Di-O-[(2,2,2-trichloroethoxy)carbonyl]baccatin III; baccatin III 13-O-acetate; baccatin diacetate; baccatin; baccatin VII; baccatin VI; baccatin IV; 7-epi-baccatin III; baccatin V; baccatin I; baccatin III; baccatin A; 10-deacetyl-7-epitaxol; epitaxol; 10-deacetyltaxol C; 7-xylosyl-10-deacetyltaxol; 10-deacetyltaxol-7-xyloside; 7-epi-10-deacetyltaxol; 10-deacetyltaxol; and 10-deacetyltaxol B.

3. A composition according to claim 1 or claim 2 wherein said taxine is selected from the group consisting of taxol and taxotere.

4. A composition according to any one of the preceding claims wherein said taxine is taxol.

5. A composition according to any one of the preceding claims wherein said triglyceride is provided by an oil which

is rich in triglycerides.

6. A composition according to claim 5 wherein said oil is selected from the group consisting of safflower and soybean oils, and mixtures thereof.

7. A composition according to claim 5 or claim 6 wherein said oil is safflower oil.

8. A composition according to any one of the preceding claims wherein said surfactant is a phospholipid.

9. A composition according to claim 8 wherein said phospholipid is lecithin.

10. A composition according to any one of the preceding claims further including an additive selected from the group consisting of a sterol and a C_{14}-C_{22} alcohol.

11. A composition according to claim 10 wherein said sterol is cholesterol.

12. A composition according to any one of the preceding claims further including glycerin.

13. A composition according to any one of the preceding claims wherein said taxine is present in an amount of about .01% to about 1% by weight of the emulsion.

14. A composition according to any one of the preceding claims wherein said triglyceride is present in an amount of about 1% to about 40% by weight of the emulsion.

15. A composition according to any one of the preceding claims wherein said surfactant is present in an amount of about 0.5% to about 5% by weight of the emulsion.

16. A composition according to claim 11 wherein said cholesterol is present in an amount of about 0% to about 1% by weight of the emulsion.

17. A composition according to claim 12 wherein said glycerin is present in an amount of about 0% to about 5% by weight of the emulsion.

18. A composition according to any one of the preceding claims wherein the emulsion contains dextrose or lactated Ringer's solution.

19. A composition according to any one of the preceding claims wherein said taxine is incorporated into said emulsion at a concentration of about 5 mg taxine/ml of said emulsion.

20. A method of incorporating a taxine into a triglyceride comprising the steps of:

dissolving a taxine in a solution of said triglyceride and a co-solvent for said taxine; and
removing said co-solvent to form a solution of said taxine in said triglyceride.

21. A method according to claim 20 wherein said taxine is selected from the group consisting of taxol; taxotere; spicatin; taxane-2, 13-dione, 5.beta., 9.beta., 10.beta.-trihydroxy-,cyclic 9, 10-acetal with acetone, acetate; taxane-2, 13-dione, 5.beta., 9.beta., 10.beta.-trihydroxy-, cyclic 9, 10-acetal with acetone; taxane-2.beta., 5.beta., 9.beta., 10.beta.-tetrol, cyclic 9, 10-acetal with acetone; taxane; cephalomannine-7-xyloside; 7-epi-10-deacetylcephalomannine; 10-deacetylcephalomannine; cephalomannine; taxol B; 13-(2', 3'-dihydroxy-3'-phenylpropionyl)baccatin III; yunnanxol; 7-(4-Azidobenzoyl)baccatin III; N-debenzoyltaxol A; O-acetylbaccatin IV; 7-(triethylsilyl)baccatin III; 7,10-Di-O-[(2,2,2-trichloroethoxy)carbonyl]baccatin III; baccatin III 13-0-acetate; baccatin diacetate; baccatin; baccatin VII; baccatin VI; baccatin IV; 7-epi-baccatin III; baccatin V; baccatin I; baccatin III; baccatin A; 10-deacetyl-7-epitaxol; epitaxol; 10-deacetyltaxol C; 7-xylosyl-10-deacetyltaxol; 10-deacetyltaxol-7-xyloside; 7-epi-10-deacetyltaxol; 10-deacetyltaxol; and 10-deacetyltaxol B.

22. A method according to claim 20 or claim 21 wherein said taxine is selected from the group consisting of taxol and taxotere.

23. A method according to any one of claims 20 to 22 wherein said taxine is taxol.

24. A method according to any one of claims 20 to 23 wherein said triglyceride is provided by an oil which is rich in triglycerides.

25. A method according to claim 24 wherein said oil is selected from the group consisting of safflower oil and soybean oil, and mixtures thereof.

26. A method according to claim 24 or claim 25 wherein said oil is safflower oil.

27. A method according to any one of claims 20 to 26 wherein said co-solvent is a short chain alcohol.

28. A method according to claim 27 wherein said short chain alcohol is selected from the group consisting of methanol, ethanol and isopropanol.

29. A method according to claim 27 or claim 28 wherein said alcohol is removed by evaporation.

30. A method according to any one of claims 20 to 29 further comprising the step of adding a surfactant.

31. A method according to claim 30 wherein said surfactant is a phospholipid.

32. A method according to claim 31 wherein said phospholipid is lecithin.

33. A method according to any one of the preceding claims comprising the further step of dispersing said taxine and triglyceride solution in water with a surfactant to form a stable oil-in-water emulsion.

34. A method according to claim 33 wherein said triglyceride is provided by an oil which is rich in triglycerides selected from the group consisting of safflower oil and soybean oil, and mixtures thereof.

35. A method according to claim 33 or claim 34 wherein said co-solvent is selected from the group consisting of methanol, ethanol and isopropanol.

36. A method according to any one of claims 33 to 35 wherein said triglyceride is provided by safflower oil, said co-solvent is isopropanol and said surfactant is lecithin.

Patentansprüche

1. Zusammensetzung zur intravenösen Verabreichung von Taxin in einer stabilen Öl-in-Wasser-Emulsion, umfassend:

   ein Taxin;
   ein Triglycerid;
   Wasser; und
   ein Tensid, wobei das genannte Taxin in dem genannten Triglycerid in einer wirksamen pharmazeutischen Menge für eine intravenöse Verabreichung aufgelöst wird, wobei das genannte Taxin und das genannte Triglycerid eine stabile dispergierte Phase in dem Wasser bilden.

2. Zusammensetzung nach Anspruch 1, bei der das genannte Taxin ausgewählt wurde aus der Gruppe bestehend aus Taxol; Taxoter; Spicatin; Taxan-2, 13-Dion, 5.beta., 9.beta., 10.beta.-trihydroxy-, zyklisch 9,10-acetal mit Aceton, Acetat; Taxan-2, 13-Dion, 5.beta., 9.beta., 10.beta.-trihydroxy-, zyklisch 9,10-Acetal mit Aceton; Taxan-2.beta., 5.beta., 9.beta., 10.beta.-tetrol, zyklisch 9,10-acetal mit Aceton; Taxan; Cephalomannin-7-xylosid; 7-epi-10-deacetylcephalomannin; 10-deacetylcephalomannin; Cephalomannin; Taxol B; 13-(2',3'-dihydroxy-3'-phenylpropionyl)baccatin III; Yunnanxol; 7-(4-Azidobenzoyl)baccatin III; N-debenzoyltaxol A; 0-acetylbaccatin IV; 7-(triethylsilyl) baccatin III; 7,10-Di-O-[(2,2,2-trichlorethoxy)carbonyl]baccatin III; Baccatin III 13-0-acetat; Baccatindiacetat; Baccatin; Baccatin VII; Baccatin VI; Baccatin IV; 7-epi-baccatin III; Baccatin V; Baccatin I; Baccatin III; Baccatin A; 10-deacetyl-7-epitaxol; Epitaxol; 10-deacetyltaxol C; 7-xylosyl-10-deacetyltaxol; 10-deacetyltaxol-7-xylosid; 7-epi-10-deacetyltaxol; 10-deacetyltaxol und 10-deacetyltaxol B.

3. Zusammensetzung nach Anspruch 1 oder Anspruch 2, bei der das genannte Taxin ausgewählt wurde aus der Gruppe bestehend aus Taxol und Taxoter.

4. Zusammensetzung nach einem der vorherigen Ansprüche, bei der das genannte Taxin Taxol ist.

5. Zusammensetzung nach einem der vorherigen Ansprüche, bei der das genannte Triglycerid durch ein Öl bereitgestellt wird, das reich an Triglyceriden ist.

6. Zusammensetzung nach Anspruch 5, bei der das genannte Öl ausgewählt wurde aus der Gruppe bestehend aus Safloröl und Sojaöl sowie Gemischen davon.

7. Zusammensetzung nach Anspruch 5 oder Anspruch 6, bei der das genannte Öl Safloröl ist.

8. Zusammensetzung nach einem der vorherigen Ansprüche, bei der das genannte Tensid ein Phospholipid ist.

9. Zusammensetzung nach Anspruch 8, bei der das genannte Phospholipid Lecithin ist.

10. Zusammensetzung nach einem der vorherigen Ansprüche, ferner umfassend ein Additiv, ausgewählt aus der Gruppe bestehend aus einem Sterol und einem C_{14}-C_{22} Alkohol.

11. Zusammensetzung nach Anspruch 10, bei der das genannte Sterol Cholesterol ist.

12. Zusammensetzung nach einem der vorherigen Ansprüche, ferner umfassend Glycerin.

13. Zusammensetzung nach einem der vorherigen Ansprüche, bei der das genannte Taxin in einer Menge von etwa 0,01 bis etwa 1 Gew.-% der Emulsion vorliegt.

14. Zusammensetzung nach einem der vorherigen Ansprüche, bei der das genannte Triglycerid in einer Menge von etwa 1 bis etwa 40 Gew.-% der Emulsion vorliegt.

15. Zusammensetzung nach einem der vorherigen Ansprüche, bei der das genannte Tensid in einer Menge von etwa 0,5 bis etwa 5 Gew.-% der Emulsion vorliegt.

16. Zusammensetzung nach Anspruch 11, bei der das genannte Cholesterol in einer Menge von etwa 0 bis etwa 1 Gew.-% der Emulsion vorliegt.

17. Zusammensetzung nach Anspruch 12, bei der das genannte Glycerin in einer Menge von etwa 0 bis etwa 5 Gew.-% der Emulsion vorliegt.

18. Zusammensetzung nach einem der vorherigen Ansprüche, bei der die Emulsion Dextrose oder laktierte Ringer-Lösung enthält.

19. Zusammensetzung nach einem der vorherigen Ansprüche, bei der das genannte Taxin in einer Konzentration von etwa 5 mg Taxin pro Milliliter der genannten Emulsion in die genannte Emulsion eingebaut wird.

20. Verfahren zum Einbauen eines Taxins in ein Triglycerid, umfassend die folgenden Schritte:

    Auflösen eines Taxins in einer Lösung des genannten Triglycerids und einem Hilfslöser für das genannte Taxin; und
    Entfernen des genannten Hilfslösers zur Bildung einer Lösung des genannten Taxins in dem genannten Triglycerid.

21. Verfahren nach Anspruch 20, bei dem das genannte Taxin ausgewählt wird aus der Gruppe bestehend aus Taxol; Taxoter; Spicatin; Taxan-2, 13-Dion, 5.beta., 9.beta., 10.beta.-trihydroxy-, zyklisch 9,10-acetal mit Aceton, Acetat; Taxan-2, 13-Dion, 5.beta., 9.beta., 10.beta.-trihydroxy-, zyklisch 9,10-Acetal mit Aceton; Taxan-2.beta., 5.beta., 9.beta., 10.beta.-tetrol, zyklisch 9,10-acetal mit Aceton; Taxan; Cephalomannin-7-xylosid; 7-epi-10-deacetylcephalomannin; 10-deacetylcephalomannin; Cephalomannin; Taxol B; 13-(2',3'-dihydroxy-3'-phenylpropionyl)baccatin III; Yunnanxol; 7-(4-Azidobenzoyl)baccatin III; N-debenzoyltaxol A; 0-acetylbaccatin IV; 7-(triethylsilyl)bac-

catin III; 7,10-Di-O-[(2,2,2-trichlorethoxy)carbonyl]baccatin III; Baccatin III 13-O-acetat; Baccatindiacetat; Baccatin; Baccatin VII; Baccatin VI; Baccatin IV; 7-epi-baccatin III; Baccatin V; Baccatin I; Baccatin III; Baccatin A; 10-deacetyl-7-epitaxol; Epitaxol; 10-deacetyltaxol C; 7-xylosyl-10-deacetyltaxol; 10-deacetyltaxol-7-xylosid; 7-epi-10-deacetyltaxol; 10-deacetyltaxol und 10-deacetyltaxol B.

22. Verfahren nach Anspruch 20 oder Anspruch 21, bei dem das genannte Taxin ausgewählt wird aus der Gruppe bestehend aus Taxol und Taxoter.

23. Verfahren nach einem der Ansprüche 20 bis 22, bei dem das genannte Taxin Taxol ist.

24. Verfahren nach einem der Ansprüche 20 bis 23, bei dem das genannte Trigylcerid durch ein Öl bereitgestellt wird, das reich an Triglyceriden ist.

25. Verfahren nach Anspruch 24, bei dem das genannte Öl ausgewählt wird aus der Gruppe bestehend aus Safloröl und Sojaöl sowie Gemischen davon.

26. Verfahren nach Anspruch 24 oder Anspruch 25, bei dem das genannte Öl Safloröl ist.

27. Verfahren nach einem der Ansprüche 20 bis 26, bei dem der genannte Hilfslöser ein kurzkettiger Alkohol ist.

28. Verfahren nach Anspruch 27, bei dem der genannte kurzkettige Alkohol ausgewählt wird aus der Gruppe bestehend aus Methanol, Ethanol und Isopropanol.

29. Verfahren nach Anspruch 27 oder Anspruch 28, bei dem der genannte Alkohol durch Verdampfung entfernt wird.

30. Verfahren nach einem der Ansprüche 20 bis 29, ferner umfassend den Schritt des Zugebens eines Tensids.

31. Verfahren nach Anspruch 30, bei dem das genannte Tensid ein Phospholipid ist.

32. Verfahren nach Anspruch 31, bei dem das genannte Phospholipid Lecithin ist.

33. Verfahren nach einem der vorherigen Ansprüche, umfassend den weiteren Schritt des Dispergierens der genannten Lösung aus Taxin und Triglycerid in Wasser mit einem Tensid zur Bildung einer stabilen Öl-in-Wasser-Emulsion.

34. Verfahren nach Anspruch 33, bei dem das genannte Triglycerid durch ein Öl bereitgestellt wird, das reich an Triglyceriden ist, die ausgewählt werden aus der Gruppe bestehend aus Safloröl und Sojaöl sowie Gemischen davon.

35. Verfahren nach Anspruch 33 oder Anspruch 34, bei dem der genannte Hilfslöser ausgewählt wird aus der Gruppe bestehend aus Methanol, Ethanol und Isopropanol.

36. Verfahren nach einem der Ansprüche 33 bis 35, bei dem das genannte Triglycerid durch Safloröl bereitgestellt wird, der genannte Hilfslöser Isopropanol und das genannte Tensid Lecithin ist.

Revendications

1. Composition pour administration intraveineuse de taxine dans une émulsion stable d'huile dans l'eau comprenant :

une taxine ;
un triglycéride ;
de l'eau ; et
un surfactant, dans laquelle ladite taxine est solubilisée dans ledit triglycéride en quantité pharmaceutique efficace pour l'administration intraveineuse, ladite taxine et ledit triglycéride formant une phase dispersée stable dans l'eau.

2. Composition selon la revendication 1, dans laquelle ladite taxine est sélectionnée dans le groupe comprenant : taxol ; taxotère ; spicatine ; taxane-2, 13-dione, 5.beta., 9.beta, 10.beta.-trihydroxy-,cyclic 9, 10-acétal avec acétone, acétate ; taxane-2, 13-dione, 5.beta-, 9.beta., 10.beta.-trihydroxy-, cyclic 9, 10-acétal avec acétone ; taxane-

2.beta., 5.beta., 9.beta., 10.beta.-tétrol, cyclic 9, 10-acétal avec acétone ; taxane ; céphalomannine-7-xyloside ; 7-épi-10-déacétylcéphalomannine; 10-déacétylcéphalomannine ; céphalomannine ; taxol B ; 13-(2', 3'-dihydroxy-3'-phénylpropionyl)baccatine III ; yunnanxol ; 7-(4-Azidobenzoyl)baccatine III ; N-débenzoyltaxol A ; O-acétylbaccatine IV ; 7-(triéthylsilyl)baccatine III ; 7,10-Di-O-[(2,2,2-trichloroéthoxy)carbonyl]baccatine III ; baccatine III 13-O-acétate ; diacétate de baccatine ; baccatine ; baccatine VII ; baccatine VI ; baccatine IV ; 7-épi-baccatine III ; baccatine V ; baccatine I ; baccatine III ; baccatine A ; 10-déacétyl-7-épitaxol; épitaxol ; 10-déacétyltaxol C ; 7-xylosyl-10-déacétyltaxol ; 10-déacétyltaxol-7-xyloside ; 7-épi-10-déacetyltaxol ; 10-déacétyltaxol ; et 10-déacétyltaxol B.

3. Composition selon la revendication 1 ou la revendication 2, dans laquelle ladite taxine est sélectionnée dans le groupe comprenant le taxol et le taxotère.

4. Composition selon l'une quelconque des revendications précédentes, dans laquelle ladite taxine est le taxol.

5. Composition selon l'une quelconque des revendications précédentes, dans laquelle ledit triglycéride est fourni par une huile riche en triglycérides.

6. Composition selon la revendication 5, dans laquelle ladite huile est sélectionnée dans le groupe comprenant les huiles de carthame et de soja, et des mélanges de ces huiles.

7. Composition selon la revendication 5 ou la revendication 6, dans laquelle ladite huile est l'huile de carthame.

8. Composition selon l'une quelconque des revendications précédentes, dans laquelle ledit surfactant est un phospholipide.

9. Composition selon la revendication 8, dans laquelle ledit phospholipide est la lécithine.

10. Composition selon l'une quelconque des revendications précédentes, comprenant en outre un additif sélectionné dans le groupe constitué d'un stérol et d'un alcool C_{14}-C_{22}.

11. Composition selon la revendication 10, dans laquelle ledit stérol est le cholestérol.

12. Composition selon l'une quelconque des revendications précédentes, comprenant en outre de la glycérine.

13. Composition selon l'une quelconque des revendications précédentes, dans laquelle ladite taxine est présente à raison d'environ 0,01% à environ 1% par poids de l'émulsion.

14. Composition selon l'une quelconque des revendications précédentes, dans laquelle ledit triglycéride est présent à raison d'environ 1% à environ 40% par poids de l'émulsion.

15. Composition selon l'une quelconque des revendications précédentes, dans laquelle ledit surfactant est présent à raison d'environ 0,5% à environ 5% par poids de l'émulsion.

16. Composition selon la revendication 11, dans laquelle ledit cholestérol est présent à raison d'environ 0% à environ 1% par poids de l'émulsion.

17. Composition selon la revendication 12, dans laquelle ladite glycérine est présente à raison d'environ 0% à environ 5% par poids de l'émulsion.

18. Composition selon l'une quelconque des revendications précédentes, dans laquelle l'émulsion contient du dextrose ou du soluté lactate de Ringer.

19. Composition selon l'une quelconque des revendications précédentes, dans laquelle ladite taxine est incorporée dans ladite émulsion en concentration d'environ 5 mg de taxine/ml de ladite émulsion.

20. Procédé d'incorporation d'une taxine dans un triglycéride comprenant les étapes de :

dissolution d'une taxine dans une solution dudit triglycéride et d'un co-solvant de ladite taxine ; et
enlèvement dudit co-solvant pour former une solution de ladite taxine dans ledit triglycéride.

21. Procédé selon la revendication 20, dans lequel ladite taxine est sélectionnée dans le groupe comprenant : taxol ; taxotère ; spicatine ; taxane-2, 13-dione, 5.beta., 9.beta, 10.beta.-trihydroxy-,cyclic 9, 10-acétal avec acétone, acétate ; taxane-2, 13-dione, 5.beta-, 9.beta., 10.beta.-trihydroxy-, cyclic 9, 10-acétal avec acétone ; taxane-2.beta., 5.beta., 9.beta., 10.beta.-tétrol, cyclic 9, 10-acétal avec acétone ; taxane ; céphalomannine-7-xyloside; 7-épi-10-déacétylcéphalomannine; 10-déacétylcéphalomannine; céphalomannine ; taxol B ; 13-(2', 3'-dihydroxy-3'-phénylpropionyl)baccatine III ; yunnanxol ; 7-(4-Azidobenzoyl)baccatine III ; N-débenzoyltaxol A ; O-acétylbaccatine IV ; 7-(triéthylsilyl)baccatine III ; 7,10-Di-O-[(2,2,2-trichloroéthoxy)carbonyl]baccatine III ; baccatine III 13-O-acétate ; diacétate de baccatine ; baccatine ; baccatine VII ; baccatine VI ; baccatine IV ; 7-épi-baccatine III ; baccatine V ; baccatine I ; baccatine III ; baccatine A ; 10-déacétyl-7-épitaxol; épitaxol ; 10-déacétyltaxol C ; 7-xylosyl-10-déacétyltaxol; 10-déacétyltaxol-7-xyloside; 7-épi-10-déacetyltaxol; 10-déacetyltaxol ; et 10-déacétyltaxol B.

22. Procédé selon la revendication 20 ou la revendication 21, dans lequel ladite taxine est sélectionnée dans le groupe comprenant le taxol et le taxotère.

23. Procédé selon l'une quelconque des revendications 20 à 22, dans lequel ladite taxine est le taxol.

24. Procédé selon l'une quelconque des revendications 20 à 23, dans lequel ledit triglycéride est fourni par une huile riche en triglycérides.

25. Procédé selon la revendication 24, dans lequel ladite huile est sélectionnée dans le groupe comprenant l'huile de carthame et l'huile de soja, et des mélanges de ces huiles.

26. Procédé selon la revendication 24 ou la revendication 25, dans lequel ladite huile est l'huile de carthame.

27. Procédé selon l'une quelconque des revendications 20 à 26, dans lequel ledit co-solvant est un alcool à courte chaîne carbonée.

28. Procédé selon la revendication 27, dans lequel ledit alcool à courte chaîne carbonée est sélectionné dans le groupe comprenant le méthanol, l'éthanol et l'isopropanol.

29. Procédé selon la revendication 27 ou la revendication 28, dans lequel ledit alcool est enlevé par évaporation.

30. Procédé selon l'une quelconque des revendications 20 à 29, comprenant en outre l'étape d'adjonction d'un surfactant.

31. Procédé selon la revendication 30, dans lequel ledit surfactant est un phospholipide.

32. Procédé selon la revendication 31, dans lequel ledit phospholipide est la lécithine.

33. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre l'étape de dispersion de ladite solution de taxine et de triglycéride dans l'eau avec un surfactant pour former une émulsion stable d'huile dans l'eau.

34. Procédé selon la revendication 33, dans lequel ledit triglycéride est fourni par une huile riche en triglycérides qui est sélectionnée dans le groupe comprenant l'huile de carthame et l'huile de soja, et des mélanges de ces huiles.

35. Procédé selon la revendication 33 ou la revendication 34, dans lequel ledit co-solvant est sélectionné dans le groupe comprenant le méthanol, l'éthanol et l'isopropanol.

36. Procédé selon l'une quelconque des revendications 33 à 35, dans lequel ledit triglycéride est fourni par l'huile de carthame, ledit co-solvant est l'isopropanol et ledit surfactant est la lécithine.